EDITORIAL

Cutaneous γδ T-Cell Lymphomas—How and Why Should They Be Recognized?

In this issue of the ARCHIVES, Toro and coworkers[1] report the clinicopathologic features of 3 adult male patients with cutaneous γδ T-cell lymphomas (CTCLs) involving the skin. These patients were distinguished by multiple plaques, tumors, and subcutaneous nodules distributed over their extremities. The lesions showed histologic evidence of epidermotropism, dermal and subcutaneous infiltration by atypical lymphocytes without cerebriform nuclei. The tumor cells had a distinct immunophenotype expressing the γδ T-cell receptor (TCR) heterodimer instead of the more common αβ TCR heterodimer. In addition, the tumor cells had a cytotoxic profile, expressing T-cell intracellular antigen 1 (TIA-1), granzyme B, and perforin. Importantly, all 3 patients with γδ CTCL had an aggressive clinical course with resistance to various chemotherapies. Similar results have been reported in the literature for patients with this uncommon type of lymphoma.[2-5]

See also page 1024

Because of its poor prognosis and resistance to chemotherapy and radiation, it is important to distinguish γδ CTCLs from mycosis fungoides (MF) and other forms of CTCL. Clinically, the presence of scaling lesions on the extremities may cause confusion with MF, but the presence of subcutaneous nodules is useful to distinguish γδ CTCL from MF. The presence of epidermotropism with a bandlike superficial dermal infiltrate in these 3 cases of γδ CTCL is similar to the histologic pattern of MF, but the lack of cerebriform cells and Pautrier microabscesses distinguishes γδ CTCL from MF. Finally, the immunophenotype of tumor cells lacking CD4 and expressing the TCRγ and TCRδ chain proteins would be exceptional for MF, in which the tumor cells have a $CD4^+$ αβ phenotype in the large majority of cases.[6]

There is some overlap of these 3 γδ CTCL cases with the variant of MF derived from $CD8^+$ cytotoxic T cells, which can have an aggressive clinical course.[7,8] Patients with the aggressive $CD8^+$ variant of MF have nodular ulcerative lesions with marked epidermotropism of tumor cells. However, unlike the current cases of γδ CTCL, a pagetoid pattern of epidermal infiltration is characteristic of aggressive $CD8^+$ MF. Moreover, the clinical involvement of palms, soles, and oral mucosa observed in aggressive $CD8^+$ MF was not observed in these 3 cases of γδ CTCLs.

The distinction of the γδ CTCLs reported herein from subcutaneous panniculitis-like T-cell lymphomas (SPTCLs) is less clear. The presence of subcutaneous nodules is a common feature of both disorders.[1-5,9] Histologically, involvement of the subcutis is the hallmark of SPTCL, whereas it was described in only 1 of these 3 cases of γδ CTCL and in nearly one half of γδ CTCLs reported in the literature (see Table 1, Toro et al). Toro et al did not observe the rimming of fat spaces by the neoplastic T cells, characteristic of SPTCL, in any of their 3 cases of γδ CTCL. This description is somewhat at variance with our experience; we observed rimming of fat spaces by atypical cells in 7 cases of SPTCL (unpublished data, 2000).[10]

The predominant clinical feature of deep-seated ulcerating lesions exposing the underlying fat is seen in both γδ CTCL and SPTCL. Another common feature of these disorders is the hemophagocytic syndrome with resulting pancytopenia, which is a life-threatening complication of SPTCL and present in more than one quarter of γδ CTCLs reported in the literature (see Table 1, Toro et al). Burg and colleagues[2] described a patient with γδ CTCL in whom the hemophagocytic syndrome was attributed to interferon gamma secreted by the neoplastic cells. We also described the hemophagocytic syndrome in a patient with γδ CTCL who had panniculitic lesions with rimming of fat spaces by neoplastic cells.[10]

As reported by Toro et al, a moderate degree of dermal involvement and epidermotropism or exocytosis of individual cells can be observed in γδ CTCL (unpublished data). In our experience, this can be coexistent with other typical features of SPTCL. However, the epidermal component appears to be more common in SPTCL with a γδ phenotype, rather than an αβ phenotype, of the neoplastic cells. This may correspond to the normal distribution and physiological features of γδ T cells.[11]

Cutaneous γδ T-cell lymphomas appear to represent a clonal expansion of γδ T cells, which normally reside in the skin and express the TCRδ variable region 2 (*Vδ2*) gene. In contrast, hepatosplenic γδ T-cell lymphomas express the *Vδ1* gene, corresponding to the predominance of normal T cells expressing *Vδ1* in the spleen.

In hepatosplenic γδ T-cell lymphomas, 2 recurrent chromosomal abnormalities have been observed: isochromosome 7q and trisomy 8 (8+).[12-14] No similar cytogenetic findings have yet been reported in primary γδ CTCL.

The cause of γδ CTCL is unknown. Toro et al did not detect Epstein-Barr viral RNA in any of the 3 cases they studied. Epstein-Barr virus has not been detected in SPTCL either. A similar experience was recorded by the European Organization for Research and Treatment

of Cancer (EORTC) Cutaneous Lymphoma Study Group (unpublished data, 2000). Toro et al suggest that long-term antigen stimulation may play a role in the cause of γδ CTCL.

The immunophenotype of γδ CTCL appears to have prognostic significance. Panniculitis-like T-cell lymphomas with an αβ phenotype have a variable prognosis. Most cases are clinically aggressive, similar to γδ CTCLs. However, a minority of αβ SPTCLs have an indolent, sometimes spontaneously remitting course.[15] Additional cases of γδ CTCL will have to be studied to determine if the prognosis is uniformly poor for this rare phenotype.

Cutaneous γδ T-cell lymphomas also should be distinguished from cutaneous natural killer (NK) cell lymphomas, which have a prominent dermal and subcutaneous component. These primary cutaneous NK cell lymphomas occur most often in men older than 50 years and present with multiple plaques that are resistant to chemotherapy.[16-18] These cases can be accompanied by a myeloproliferative disorder, myelodysplasia, or a leukemic phase of the NK cell lymphoma.[17,18] The NK tumor cells are generally larger than those of γδ CTCLs, have a $CD56^+$ phenotype, and are commonly $CD4^+$, which is exceptional for γδ CTCLs.

Toro et al suggest that γδ CTCL should be included in the category of peripheral T-cell lymphomas, not otherwise specified, in the Revised European-American Lymphoma (REAL)[19] Classification. In my opinion, these γδ CTCLs deserve special recognition, although they may not fit into the current classification schemes for systemic lymphomas. It has already been suggested that the REAL Classification may not be adequate to encompass all cutaneous lymphomas that appear to have distinctive biological features, clinical course, and prognosis when compared with systemic lymphomas.[3] For example, follicular center cell lymphomas in the skin generally are localized tumors that lack the bcl-2 oncoprotein characteristic of systemic follicular lymphomas.[20-22] They recur locally without systemic spread, whereas systemic or nodal follicular center cell lymphomas are generally widely disseminated tumors involving the bone marrow. Primary cutaneous $CD30^+$ lymphomas are also distinctive from their systemic counterpart. The systemic $CD30^+$ lymphomas occur predominantly in children and are associated with a recurrent translocation, t(2;5)(p23;q25), with resultant expression of an anaplastic lymphoma kinase oncoprotein that drives the proliferation of the neoplastic cells.[23-26] The primary cutaneous $CD30^+$ lymphomas almost always lack the anaplastic lymphoma kinase oncoprotein, occur mainly in adults, and have a much more favorable prognosis than systemic $CD30^+$ lymphomas.[27-30] Certainly, hepatosplenic γδ T-cell lymphomas have proven to be distinct from other peripheral T-cell lymphomas in clinical course, histopathological features, cause, and prognosis.[5,9,12-14,19] Thus, it is likely that a distinct group of primary γδ CTCLs will emerge as a clinicopathologic entity with a specific chromosomal or molecular genetic marker involved in the pathogenesis. Such cases will have to be distinguished from SPTCL, pagetoid reticulosis, and MF with a γδ phenotype.[31-33] Hopefully, distinction of different subtypes of primary γδ CTCLs will lead to a better understanding of their pathophysiological features and result in more effective therapy.

Marshall E. Kadin, MD
Department of Pathology
Beth Israel Deaconess Medical Center and Harvard Medical School
330 Brookline Ave
Boston, MA 02215
(e-mail: mkadin@ caregroup.harvard.edu)

REFERENCES

1. Toro JR, Beaty M, Sorbara L, et al. γδ T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. *Arch Dermatol.* 2000;136:1024-1032.
2. Burg G, Dummer R, Wilhelm M, et al. A subcutaneous delta-positive T-cell lymphoma that produces interferon gamma. *N Engl J Med.* 1991;325:1078-1081.
3. Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. *Blood.* 1997;90:354-371.
4. Arnulf B, Copie-Bergman C, Delfau-Larue MH, et al. Nonhepatosplenic γδ T-cell lymphoma: a subset of cytotoxic lymphomas with mucosal or skin localization. *Blood.* 1998;91:1723-1731.
5. Przybylski GK, Wu H, Macon WR, et al. Hepatosplenic and subcutaneous panniculitis-like γ/δ T cell lymphomas are derived from different Vδ subsets of γ/δ T lymphocytes. *J Mol Diagn.* 2000;2:11-19.
6. Ralfkiaer E, Wollf-Sneedorff A, Thomsen K, Geisler C, Lange Vejlsgaard GL. T-cell receptor γδ-positive peripheral T-cell lymphomas presenting in the skin: a clinical, histological and immunophenotypic study. *Exp Dermatol.* 1992;1:31-36.
7. Agnarsson BA, Vonderheid EC, Kadin ME. Cutaneous T cell lymphoma with suppressor/cytotoxic (CD8) phenotype: identification of rapidly progressive and chronic subtypes. *J Am Acad Dermatol.* 1990;22:569-577.
8. Berti E, Tomasin D, Vermeer MH, et al. Primary cutaneous CD8-positive epidermotropic cytotoxic T-cell lymphomas: a distinct clinicopathologic entity with aggressive clinical behavior. *Am J Pathol.* 1999;155:483-491.
9. Gonzalez CL, Medeiros MJ, Braziel RM, et al. T-cell lymphoma involving subcutaneous tissue: a clinicopathologic entity commonly associated with hemophagocytic syndrome. *Am J Surg Pathol.* 1991;15:17-27.
10. Levi E, Kadin ME. *Panniculitic Gamma-Delta T-Cell Lymphoma: Quarterly Case Study of the Society of Hematopathology.* Fripp Island, SC: Society for Hematopathology; May 1997.
11. Alaibac M, Daga A, Harms G, et al. Molecular analysis of the gamma delta T-cell receptor repertoire in normal human skin and in Oriental cutaneous leishmaniasis. *Exp Dermatol.* 1993;2:106-112.
12. Kadin ME, Kamoun M, Lamberg J. Erythrophagocytic T γ lymphoma: a clinicopathologic entity resembling malignant histiocytosis. *N Engl J Med.* 1981;304:648-653.
13. Cooke CB, Krenacs L, Stetler-Stevenson M, et al. Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic γδ T-cell origin. *Blood.* 1996;88:4265-4274.
14. Salhany KE, Feldman M, Kahn MJ, et al. Hepatosplenic gamma delta T-cell lymphoma: ultrastructural, immunophenotypic, and functional evidence for cytotoxic T lymphocyte differentiation. *Hum Pathol.* 1997;28:674-685.
15. Salhany KE, Macon WR, Choi JK, et al. Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. *Am J Surg Pathol.* 1998;22:881-893.
16. Wasik MA, Sackstein R, Novick D, et al. Cutaneous $CD56^+$ large T-cell lymphoma associated with high serum concentration of IL-2. *Hum Pathol.* 1996;27:738-744.
17. DiGiuseppe JA, Louie DC, Williams JE, et al. Blastic natural killer cell leukemia/lymphoma: a clinicopathologic study. *Am J Surg Pathol.* 1997;21:1223-1230.
18. Chan JK, Sin VC, Wong KF, et al. Nonnasal lymphoma expressing the natural killer marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. *Blood.* 1997;89:4501-4513.
19. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood.* 1994;84:1361-1392.
20. Willemze R, Meijer CJ, Sentis HJ, et al. Primary cutaneous large cell lymphomas of follicular center cell origin: a clinical follow-up study of 19 patients. *J Am Acad Dermatol.* 1987;16:518-526.

21. Santucci M, Pimpinelli N, Arganini L. Primary cutaneous B-cell lymphomas: a unique type of low-grade lymphoma: clinicopathologic and immunologic study of 83 cases. *Cancer*. 1991;67:2311-2326.
22. Cerroni L, Volkenandt M, Rieger E, Soyer HP, Kerl H. bcl-2 protein expression and correlation with the interchromosomal 14;18 translocation in cutaneous lymphomas and pseudolymphomas. *J Invest Dermatol*. 1994;102:231-235.
23. Kadin ME, Sako D, Berliner N, et al. Childhood Ki-1 lymphoma presenting with skin lesions and peripheral lymphadenopathy. *Blood*. 1986;68:1042-1049.
24. Shiota M, Fujimoto J, Takenaga M, et al. Diagnosis of t(2;5)(p23;q35)-associated Ki-1 lymphoma with immunohistochemistry. *Blood*. 1994;84:3648-3652.
25. Nakagawa A, Nakamura S, Ito M, Shiota M, Mori S, Suchi T. CD30-positive anaplastic large cell lymphoma in childhood: expression of p80npm/alk and absence of Epstein-Barr virus. *Mod Pathol*. 1997;10:210-215.
26. Morris S, Kerstein M, Valentine M, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science*. 1994;263:1281-1284.
27. Beljaards RC, Kaudewitz P, Berti E, et al. Primary cutaneous CD30-positive large cell lymphoma: definition of a new type of cutaneous lymphoma with a favorable prognosis: a European multicenter study of 47 cases. *Cancer*. 1993;71:2097-2104.
28. Paulli M, Berti E, Rosso R, et al. CD30/Ki-1-positive lymphoproliferative disorders of the skin—clinicopathologic correlation and statistical analysis of 86 cases: a multicentric study from the European Organization for Research and Treatment of Cancer Cutaneous Lymphoma Project Group. *J Clin Oncol*. 1995;13:1343-1354.
29. DeCoteau JF, Butmarc JR, Kinney MC, Kadin ME. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30$^+$ lymphoproliferative disorders: comparison with anaplastic large cell lymphoma of nodal origin. *Blood*. 1996;87:3437-3441.
30. Vergier B, Beylot-Berry M, Pulford K, et al. Statistical evaluation of diagnostic and prognostic features of CD30$^+$ cutaneous lymphoproliferative disorders: a clinicopathologic study of 65 cases. *Am J Surg Pathol*. 1998;22:1192-1202.
31. Barzilai A, Goldberg I, Shibi R, Kopolovic J, Trau H. Mycosis fungoides expressing a gamma/delta T-cell receptor. *J Am Acad Dermatol*. 1996;34:301-302.
32. Berti E, Cerri A, Cavicchini S, et al. Primary cutaneous gamma/delta T-cell lymphoma presenting as disseminated pagetoid reticulosis. *J Invest Dermatol*. 1991;96:718-723.
33. Munn SE, McGreagor JM, Jones A, et al. Clinical and pathological heterogeneity in cutaneous gamma-delta T-cell lymphoma: a report of three cases and a review of the literature. *Br J Dermatol*. 1996;135:976-981.